REMARKS

The Office Action dated March 10, 2004 has been received and carefully studied.

A Request for Continued Prosecution is filed herewith.

The Examiner rejects claims 13 and 17-19 under 35 U.S.C. §103(a) as being unpatentable over Bussey, U.S. Patent No. 6,011,148 in view of Geiger et al., U.S. Patent No. 5,589,342. The Examiner states that Bussey teaches a process of ultrafiltration of nucleic acids using differential pressure as a driving force, from a liquid sample by diluting the sample. The Examiner admits that Bussey does not teach fractionation of DNA fragments, but states that the instant application only describes the process of purifying DNA fragments using ultrafiltration with increased recovery by dilution of the sample, even though the application recites the process as "fractionation".

By the accompanying amendment, claims 17-19 have been cancelled in order to simply the issues and expedite allowance. Also by the accompanying amendment, claim 13 has been amended to recite a process for the improved recovery of small fragment double stranded linear nucleic acids having less than about 300 base pairs.

Bussey concerns large-scale tangential flow filtration (TFF) in which the sample being filtered is constantly being diluted. In contrast, claim 13 recites diluting the liquid sample, and subsequently contacting the diluted sample with an ultrafiltration membrane. This is not TFF. Furthermore Bussey separates unlike species. Claims 13 recites a process for improved recovery of double stranded linear nucleic acids from a sample consisting essentially of linear nucleic acids, thereby excluding from that sample unlike species. Stated differently, the dilution step of Bussey is to remove contaminants that are not present

in any significant amount in the instant sample (as excluded by the "consisting essentially of" language). Applicants therefore respectfully submit that the skilled artisan would not be motivated to modify Bussey to arrive at the instant invention as claimed. Since Bussey's objective in *continuously* diluting the sample is very different, one skilled in the art would not be motivated to modify Bussey and arrive at the present invention.

Submitted herewith as an Appendix is a graph of the predicted retention of small DNA as a function of time and salt concentration using the TFF of Bussey, and a graph of the predicted retention of small DNA as a function of time and salt concentration using a single dilution step and continuous pressure differential ultrafiltration as in the present invention. Because Bussey operates in a continuous diafiltration mode, diluent is continuously added over the entire course of the filtration. This necessarily changes the salt concentration, making the rate of small fragment DNA loss very high at the beginning of the process when the salt concentration is the highest. Since so much small fragment DNA is lost while the salt concentration is high, improved recovery thereof cannot be obtained. In contrast, filtration does not begin in the instant process until the salt concentration is low due to the single step dilution. Loss of small fragment DNA is thus minimized.

The Examiner rejects claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over Bussey in view of WO 00/66723 and Geiger '342, and claims 9-12 as being unpatentable over Bussey in view of Simon and Geiger '342. WO 00/66723 is cited for its disclosure of ultrafiltration to dryness of nucleic acid samples with membranes. Geiger '342 is newly cited for its teaching that both single-stranded and double-stranded nucleic acids are commonly believed to be linear polymers. Simon is cited as disclosing

monovalent and bivalent cations for removal of contaminants by centrifugal ultrafiltration. The Examiner concludes that it would have been obvious to filter the Bussey sample to dryness, to use the Simon cations in the Bussey process, and that the DNA of Bussey is linear.

By the accompanying amendment, the independent claims have been amended to recite a process for the improved recovery of small fragment double stranded linear nucleic acids.

The Examiner states that since Bussey uses the same method of dilution, the same differential pressure and a similar ultrafiltration membrane, it would be obvious to one skilled in the art that the process taught by Bussey also would provide the same recovery of nucleic acid fragments as in the instant application. However, Bussey does not use the same method of dilution. As articulated above, Bussey uses tangential flow filtration, which requires continuous dilution during the entire filtration process. This necessitates filtering sample where the salt concentration is substantially higher at the start of the filtration than at the end, which inherently results in a significant loss of small fragment DNA as illustrated in the attached Appendix.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,

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